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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE
DISEASES OF INFANTS AND CHILDREN
JOHN FITCH LANDON, M.D., Editor

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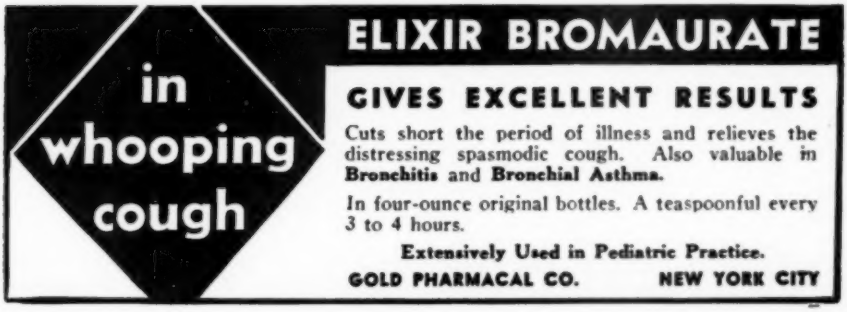
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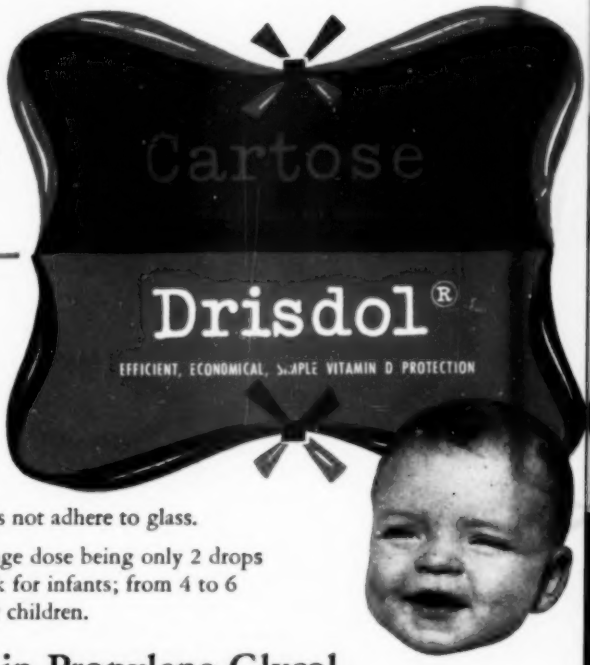

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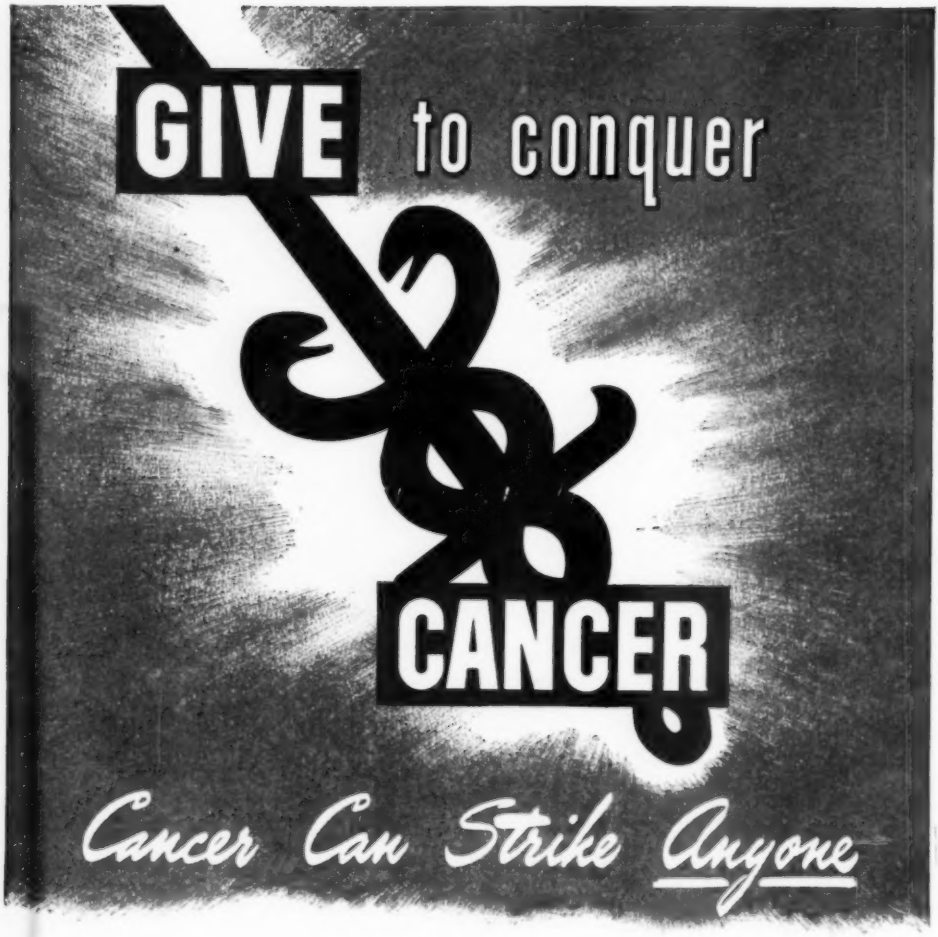

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* Jones, C. M., Culver, P. J., Drummey, G. D., and Ryan, A. E.: Ann. Int. Med. 29:1,1948.

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(1) Frisk, A. R., et al: Brit. Med. J. 1:7, 1947; (2) Ledbetter, J. H., and Cronheim, G. E.: Am. J. Med. Sci. 216:27, 1948.

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VOL. 66 MAY 1949 No. 5

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THE THERAPEUTIC AND PROPHYLACTIC ADMINISTRATION OF WHEAT GERM OIL (VITAMIN E) IN INFANCY AND CHILDHOOD*

SIMON STONE, M.D.
Manchester, N. H.

The actual need for vitamin E as a dietary supplement in humans has not yet been established. In experimental animals, however, Evans and Burr[1] were first to demonstrate that deficiency of vitamin E in the diet of the pregnant rat will result in paralysis of extremities in the offspring. Feeding of wheat germ oil during the last period of pregnancy or even within two weeks after birth[2] will avert paralysis in the majority of the newborn probably as a result of transmission of protective substances through lactation. Muscular lesions, similar to those observed in cases of muscular dystrophy in humans, have been produced by Goettsch and Pappenheimer[3] in guinea pigs and rabbits on a vitamin E deficient diet. MacKenzie and McCollum[4] were able to cure muscular dystrophy in the rabbit or prevent its occurrence by therapeutic and prophylactic administration of alpha tocopherols.

The results from clinical application of vitamin E in the growing child was described previously[5] in cases of myatonia congenita and muscular dystrophy, muscular hypotonia and hypoplasia and in cases of anterior poliomyelitis with mild to moderate muscle weakness. It was assumed that a deficiency of certain

* From the Neurological Service of the Elliot Hospital, Manchester, N. H. and the Crippled Children's Services of the State of New Hampshire.

dietary factors needed for proper muscular development, or inability to transmit them to the offspring, existed in the pregnant mother in cases of muscular dystrophy and myatonia congenita. The failure to have this inadequacy remedied after birth, either because of the reduced vitamin E contents of the milk fed the newborn or faulty utilization, resulted in the development of the above conditions in varying severity. It is more likely, however, that the beneficial effects from the administration of the vitamin E factors is not in all instances due to replacement of a deficiency, but is a result of the nonspecific effect of the vitamin on muscle growth and muscle tone.

The present report deals with results obtained from the administration of wheat germ oil and wheat germ oil concentrates when administered alone, or in combination with other vitamins, to a large group of children with a variety of neurological and neuromuscular disorders and also to "normal" children with slightly below par muscular development. These children were observed in the Crippled Children's Clinics of the State of New Hampshire, on the Neurological Service of the Elliot Hospital and the author's private practice. For the last 10 years over 300 cases have been treated and the following conditions are included: Muscular dystrophies; myatonia congenita; muscular hypotonia; congenital nonobstructive hydrocephalus; anterior poliomyelitis with residual muscular weakness; mongolism and cretinism; cerebral palsy states.

METHOD OF ADMINISTRATION

Wheat germ oil (Lilly) was used in most instances to supply the vitamin E factors, except in older children where natural mixed tocopherols were substituted for the wheat germ oil because of gustatory objections. The average dose for infants and younger children was 1 cc. of the oil for every 10-15 pounds of body weight, or 3-10 mg. of mixed tocopherols for every 10 pounds of weight in older children. The oil was administered either alone or in a mixture with malt and vitamin concentrates (Avimal). Preparations containing iron were avoided because of the incompatibility of the tocopherols with iron salts. The oil was mixed with this malt combination without the use of an emulsifying agent. The mother was instructed to stir the mixture thoroughly before administration and to keep it in a cool place. Fifteen to sixty cc. of

the oil have been mixed satisfactorily with 240 cc. of the malt mixture without impairing its palatability, and this combination is well taken by most children. One to three teaspoonfuls daily is the average dosage, the ratio of the oil in the mixture being increased for the older children. No complications have been observed in any of the cases from the administration of the oil except for a skin rash on rare occasions, which usually disappeared in a few days following discontinuance of medication.

CONDITIONS TREATED

Muscular Dystrophies. This group includes 25 children with various types of muscular dystrophy. When children with dystrophies were first placed under treatment in 1938, they were given 1-4 cc. of wheat germ oil daily in a mixture with vitamin B complex. Nearly all of them showed definite improvement when on this regime. A few relapsed after a time because of the family's failure to continue with the administration of the medication regularly, and several relapsed for unexplained reasons. Some children treated at a later date, however, failed to show even this initial gain. The reason for discrepancy in the results was sought and the following explanation has suggested itself: The children who were first placed under treatment received the oil in a mixture with vitamin B complex in a malt base which also contained vitamin C. In the process of later manufacture the vitamin C was omitted by the manufacturer, and some of the children treated with the same mixture without the vitamin C failed to show the expected improvement. Since then vitamin C has been routinely administered with the wheat germ oil and maintenance doses of other vitamins, and results have been more promising. The sporadic cases appeared to respond better than those of hereditary origin, and even in the latter cases the downhill course appeared to be retarded by above medication including 100-150 mg. of vitamin C daily. The pseudohypertrophic cases responded better than other types, and the improvement appeared greater when the treatment was instituted before atrophy had set in. Omission of medication for a few weeks was observed to result in considerable reduction in muscle strength and inability to carry on with usual activities. One youngster, who has been enabled to walk to school daily while receiving this vitamin mixture regularly, is hardly able to walk

any distance when it is temporarily discontinued and walks better when its administration is resumed. Failure to regain former status was observed, however, after the medication was discontinued for a longer period of time, and doubling or tripling the amount of wheat germ oil these children were receiving was just as ineffective.

It is probable that muscular dystrophy is a metabolic disorder manifested in faulty utilization of certain amino acids and impairment of muscle metabolism, and concomitant disturbance of muscle cell oxidation processes. Oxygen consumption has been shown by Houchin and Mattill[6] to rise about 250 per cent in the dystrophic muscle with a drop to normal values within 24 hours after alpha tocopherol administration. This restoration of dystrophic muscle oxygen consumption in vitro to normal by the addition of vitamin E would point to the latter as an important regulator of tissue oxygen utilization, probably acting through a different enzyme system than thiamine. The large contents of vitamin E in the pancreas and the importance of pancreatic secretion in fat and protein metabolism would suggest the possibility that a deficiency of pancreatic proteolytic enzymes is a contributing cause to the development of muscle dystrophy.[5] Milhorat and Bartels[7] have also reported on the greater effectiveness of vitamin E when combined with inositol in the treatment of muscular dystrophies. It is probable that milder cases can benefit from vitamin E administration alone, while the more severe cases require an extra, as yet undetermined, factor besides the vitamin E for maximum therapeutic effects. Until the exact nature of this factor is determined, wheat germ oil or natural mixed tocopherol concentrates in combination with other vitamins would appear the most effective therapy for muscular dystrophy for the present.

Myatonia Congenita. The administration of vitamin E in the same dosage with the polyvitamin mixture described above has produced palpable contractile muscle tissue in children where none was in evidence before treatment was begun. The previously accepted assumption that children with myatonia congenita recover spontaneously has not been borne out by observation in our clinic in cases of long standing. In several such instances a diagnosis of myatonia congenita was made elsewhere by competent clinicians, and these children, when re-examined at this clinic several years

later, failed to show any appreciable improvement through the intervening years. Infants and younger children who exhibited no voluntary movements and had no palpable contractile musculature, after 2-3 months of wheat germ oil therapy were able to turn over voluntarily, hold up their heads and reach out for toys. Normally contracting muscle tissue could be felt where there was none previously. The results were least impressive in cases of long standing and most promising when the child was placed under treatment during the first year of life.

Muscular Hypotonia. I have included in this group many of the children frequently seen by the pediatrician, with poorly developed, flabby musculature, diminished muscle strength and tone, impaired posture, with winging of scapulae and pronated feet, and reduced or absent deep reflexes. The child is usually seen after the parents have become aware of the retardation in motor development, as manifested in the infant's inability to hold up his head or turn over without aid at a late age, and considerable delay in standing or walking time. Postnatal nutritional deficiency is probably the etiologic factor in the majority of cases, a few belong in the aborted myatonia congenita group, some are of cerebral atonia origin, and I have seen several at a later age develop into Friedreich's ataxia. Most all of them have received mixed vitamin therapy in some form in the past, outside of vitamin E, without any impressive gain. Wheat germ oil in the dosage previously described when added to the other vitamins these children were receiving has hastened the appearance of palpable, normally contracting musculature with concomitant improvement of muscle tone and strength and produced acceleration of motor maturation. A gain in intelligence and mental alertness was also frequently reported by the parents while these children were under treatment.

Congenital Nonobstructive Hydrocephalus and Spina Bifida. The results from administration of wheat germ oil to infants and young children with nonobstructive hydrocephalus has been previously reported.[8] Decrease in rate of expansion of skull circumference was observed in nearly all cases, with improvement in general health and mental alertness. In instances where the hydrocephalus was combined with spina bifida, it became possible to close up the spina bifida after the infant was placed on wheat germ oil without aggravation of the condition of the hydrocephalus.

One to four cc. of wheat germ oil daily was the average dose in combination with other vitamins.

Anterior Poliomyelitis. I have used wheat germ oil routinely in combination with a polyvitamin mixture of vitamins A, B complex, C and D in all infants and younger children with anterior poliomyelitis.[9] The more severely affected cases also received intraspinal pyridoxine thiamine therapy and artificial fever, the latter being used mainly in the more severely paralyzed cases with reflex muscle rigidity and severe discomfort on motion. In older children mixed tocopherols capsules were used, about 1 mg. per kg. of body weight daily. This was also combined with multivitamin capsules containing at least 10,000 units of vitamin A, 1,000 units of vitamin D, 10 mg. of thiamine, 3 mg. of pyridoxine, 10 mg. of panthotenic acid and 50 mg. of niacinamide, daily. While it is rather difficult to evaluate response to oral therapy because the improvement is not as immediate as that observed following parenteral medication, the recovery in a number of children who received no other treatment but physiotherapy appeared to be hastened by this medication. These children appeared to show a more rapid return of muscle tone and strength, displayed a desire to get up earlier because of the improvement in their sense of well-being and general health.

Mongolism and Cretinism. A total of twelve cases of mongolism have been treated to date. Outside of the typical facies and mental retardation, muscular hypotonia or atonia has been one of the characteristic symptoms of this disorder. Definite improvement in muscle strength and muscle tone has been observed in all these patients under wheat germ oil therapy with suggestive acceleration of their motor development. Their muscle tone, however, while greatly improved, still remained subnormal. In the past the hypotonia in mongolism was suspected by some observers to be caused by cerebellar hypoplasia, but the improvement under vitamin E therapy would suggest that this hypotonia is of endocrine and metabolic origin. The improvement in intelligence, however, was not as pronounced in this group of cases as the physical gain. In cases of cretinism it was combined with thyroid therapy with greater effectiveness. The importance of an adequate vitamin E intake in prevention of thyroid and pituitary atrophy in experimental animals has been previously reported.[10]

Whether a vitamin E deficiency in the pregnant mother is responsible for the hypoplasia of certain endocrine glands in the human newborn is problematical.

Cerebral Palsy States. General gain in muscle strength, general health, mental alertness and sense of well-being, with a minor effect on the spasticity, was observed in the cases treated. The purely spastic cases seemed to do better than the athetoid or the ataxic states.

So-called "Normal" Children. In the crippled children clinics a number of children are seen annually without any definite orthopedic or neurologic problems. They are brought to the clinic because they fatigue easily, display poor posture, show some pronation of feet, are listless in school. An orthopedic or neurologic problem is suspected by the teacher or school nurse, but these children show no definite pathology on physical checkup except for flabby musculature, winging of scapulae, protrusion of abdomen, and many are also underweight with little subcutaneous fat. Some are obese, but with little palpable contractile musculature under the fat layer. A number of them responded to improvement in nutritional status, postural exercises, increased vitamin intake. The gain, however, appeared much more rapid, especially in regard to muscle tone and muscle strength, after the addition of wheat germ oil in infants or natural mixed tocopherols in older children to the vitamins these children were already receiving. A concomitant improvement in the intelligence of these children, as evidenced in more efficient performance in their school work, was also confirmed by psychological tests in selected cases.

COMMENT

In view of the wide distribution of tocopherols (vitamin E) in vegetable and animal tissues it has been assumed in the past that the need for vitamin E in the body is probably not as great as it is for other vitamins and that a vitamin E deficiency does not exist, or the results of the deficiency are not as obvious as it is with other vitamins. The actual requirements for most of the other vitamins has been simpler to estimate because of the development of definite clinical syndromes following inadequate intake or their faulty absorption from the diet, and the disappearance of symptoms after the vitamin lack has been corrected. So far, how-

ever, no definite clinical syndrome has been established as a result of vitamin E deprivation in humans, although in animals several neuromuscular syndromes have been associated with a vitamin E free diet. It has been estimated, however, that the daily tocopherol requirements for maintenance of body needs at a normal level for infants is the equivalent of 2-15 mg. of alpha tocopherol daily; in children 15-120 mg. daily; and for adults 20-170 mg. per day, depending on the pre-existent state of tocopherol saturation. The average intake, however, even in a diet rich in vitamin E is only about one-fifth of the maximum daily requirements, and this just about supplies the necessary amount to maintain an average level in the body, provided no extra drain on tocopherols is made as would follow a diet containing rancid fat or iron salts.

The favorable response to vitamin E therapy in neuromuscular disorders in children is suggestive that conditions like amyotonia congenita and certain muscular dystrophies might represent analogous disorders to that observed in the offspring of animals on an E deficient diet. However, the fact that a certain disorder responds well to vitamin administration does not always imply that an inadequate intake of this vitamin is the etiologic factor. Beyond a certain saturation point a vitamin becomes a drug with a selective action on certain body tissues, similar to that of digitalis on cardiac muscle or prostigmin on acetylcholine utilization in myasthenia gravis, irrespective of the presence of a deficiency of this vitamin.

A number of facts are apparent from experimental studies and the result of therapeutic applications of vitamin E. It is synergistic with fat soluble vitamin A[11] and when added to the latter in experimental animals will augment growth, produce gain in weight, and also increase the amount of vitamin A stored in the liver. Maximum utilization of vitamin A and carotene probably depends also on the presence of optimum supply of vitamin E.[12]

Vitamin E is also an important factor in utilization and storage of fat[13] in the body and in the sparing of proteins by preventing their too rapid breakdown in animals on a low protein diet.[14] When added to fats it will prevent rancidity in vitro as well as in vivo. The fat of animals fed on an increased tocopherols intake remains fresh longer after slaughtering, and does not become

rancid as fast as fat of animals not receiving added vitamin E. However, while vitamin E as an anti-oxidant prevents rancidity from developing, it is also destroyed in the process and therefore vitamin E deficiency will develop if the animal is fed an excessive amount of rancid fat. Because of its action as anti-oxidant it is probably related to the enzyme systems of the body involved in fat and protein metabolism and acts by increasing or slowing down oxygenation as the body-needs demand. The excessive consumption of oxygen in dystrophic muscle[15] and the return to normal oxygenation on an ample tocopherol intake would point to vitamin E as a regulator of oxidation thus preventing too rapid breakdown of tissues.

If one wishes to generalize about the place of some of the known vitamins in body metabolism and their utilization by various tissues in the living organism, it would appear that vitamin A is utilized by the epithelial (ectodermal) structures in the body, vitamin B factors are needed for proper function of nervous tissue, vitamin C is necessary for maintenance of the integrity of vascular system and collagen matrix, and vitamin D for proper development of osseous tissues. Vitamin E according to this hypothesis is required by mesenchymal derivatives which includes muscle tissue, blood vessels, collagen matrix and connective tissue of the body. It is synergistic in its action with other vitamins either through augmenting their activity or by having a sparing effect so that lesser amounts will be required of these vitamins. Its relation to vitamin A has been previously pointed out. In cases of vitamin B factors it affords extra protection against demyelinization and the breakdown of lipoid lining of nerve fibres; and to vitamin C in aiding of maintenance of normal collagen matrix in the body. Chemically it is closely related to vitamin K and the place of vitamin E in relation to cellular permeability and hemorrhage has been reported by Dam[16] and Mason.[17] The addition of vitamin E to the other vitamins not only increases their effectiveness, but also acts as a sparing agent so lesser amounts of these vitamins are required for the maintenance of the integrity of the body.

The greater need for vitamin E in the young, growing organisms has been previously pointed out.[5] Quaife[18] has demonstrated an increase in the vitamin E contents of maternal milk shortly after

birth with reduction in contents in later samples, and also a greater transfer of vitamin E from the tissues into the maternal blood during the latter part of pregnancy.[19] This would suggest that the newborn requires greater amounts of this vitamin because of its protective function and its aid in growth and tissue metabolism. In cases where the human newborn depends entirely on cow's milk for food, the chances are that the contents of vitamin E in milk supplied through regular channels would be inadequate to supply all requirements of the newborn for this vitamin for the reason that the vitamin E content of cow's milk is richest after delivery and is diminished gradually, and the commercial milk supply usually is derived from animals long freshened.

The impressive response of children with selected neuropsychiatric and neuromuscular disorders to vitamin E therapy, would suggest that the rapidly growing organism needs greater amounts of this vitamin for optimum development. In my experience the so called "normal state of well-being" in many children can be vastly improved by the addition of this vitamin to their diet. A number of children, it would appear, require greater amounts of this vitamin either for the reason of their inability to utilize fully the supply present in their diet, provided their diet is adequate, or because it acts as a nonspecific tissue activator. Although most children in previous generations have gotten along, after a fashion, without any addition of cod liver oil or vitamin B complex factors to their diet without developing deficiency symptoms, the widespread supplementation of the average diet with these vitamins has brought forth general improvement in the health of the American child. At present vitamin supplements have become a standard part of our dietary and several B complex factors are mixed with the flour by the baker in bread-making, irrespective of the presence of clinical evidence of even a mild deficiency in the population. In view of the removal of wheat germ in modern milling, it would therefore appear important to include vitamin E also as a dietary supplement, preferably as wheat germ oil in all children, but especially in those who are lagging in their neuromuscular and endocrine development, in those showing evidence of disturbance of fluid metabolism in the body, or lowered intelligence without any definite neurological or psychiatric etiology. I have seen no harm from its administration for a period of 10

years in a great number of children, and I feel that its administration is just as safe as vitamin A, or vitamin B complex, and a great deal safer as far as danger from overdosage is concerned than vitamin D.[29] The dosage should vary from a maintenance dose of about ½ cc. of wheat germ oil or 1 mg. of natural mixed tocopherols per 10 pounds of body weight for the so-called "normal" child with slightly below par muscular development, to 1-2 cc. of wheat germ oil, or 3-10 mg. of mixed tocopherols per 10 pounds of body weight for the child with evidence of neuromuscular dysfunction, early hydrocephaly, endocrine underdevelopment, and below par general intelligence without any demonstrable cause.

SUMMARY AND CONCLUSIONS

Vitamin E in the form of wheat germ oil or wheat germ oil concentrates has been administered for the last 10 years to a large group of children with a variety of neuromuscular disorders and other disturbances of the nervous system. It was effective when combined with other vitamins in arresting or retarding the downhill progress of a number of patients with muscular dystrophy. It produced increase in muscle tissue proliferation and improvement in muscle tone in cases of myatonia congenita, and in cases of retarded motor maturation and muscular underdevelopment of unknown etiology in the young. In anterior poliomyelitis and infectious polyneuritis with residual mild to moderate muscle atrophy, its administration produced increase in the sense of well-being in these patients and seemed to hasten regeneration of atrophied musculature.

In cases of non-obstructive congenital hydrocephalus it produced arrest or reduction of rate of skull expansion except in fulminating cases, brought forth decrease of intensity of nystagmoid movements of eyes and hastened motor maturation. Cases of mongolism and cretinism responded to vitamin E administration by showing improvement in muscle strength and muscle tone and some increase in mental alertness, especially in cases of cretinism when combined with thyroid extract.

Improvement in general health, muscle tone and increase in alertness and general intelligence, the latter as evidenced in psychometric tests in selected cases, has been observed in a large group

of so-called "normal" children with below par muscular development and retarded intelligence probably of nutritional origin.

It is suggested that vitamin E is required for the maintenance of the integrity of the mesenchymal tissues of the body, is important in fat and protein metabolism and is synergistic in its action with other vitamins, especially vitamin A, selected vitamin B complex factors, and vitamins C and K. The administration of vitamin E is safe and should be included as a regular dietary supplement with all vitamin mixtures in view of the inadequate contents of the average diet in vitamin E.

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EARLY DYSPLASIAS OF THE HIP

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Dysplasia of the hip is a congenital anomaly where there is an incongruity between the head of the femur and the acetabulum. In a perfect attitude there is a concentric relation between the concave surface of the acetabulum and the globular head of the femur which permits free circumferential movement within the limits allowed by the soft structures surrounding the hip.

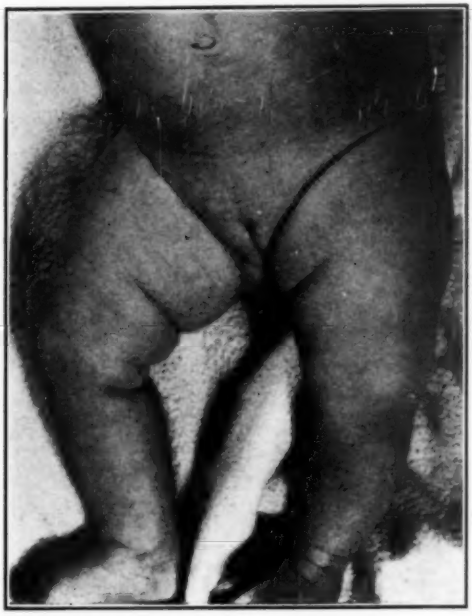

Fig. 1. The attitude of the right extremity is everted and moderately abducted with the foot turned out. The affected left extremity is moderately adducted, slight bowing at the knee and the foot is inverted.

In European countries, particularly in northern Italy and Czechoslovakia, hip distortions are very prevalent. Putti[1] has written

extensively about this phenomenon. Many contributions have been made by German and Swedish authorities. The American literature is sparse. Hart[2] made a valuable contribution giving his own observations and quoting freely from the European literature.

Dysplasias are classified in two types: subluxation and luxation. In the former the distorted head of the femur imperfectly articulates within the hip joint. This type may adjust its process and heal spontaneously. If the incongruity remains, it acts in the same manner as a partially worn down brake lining which results in a wear-down of the articular cartilage which Nature tries to repair, frequently not too successfully. The result is an arthritis which is

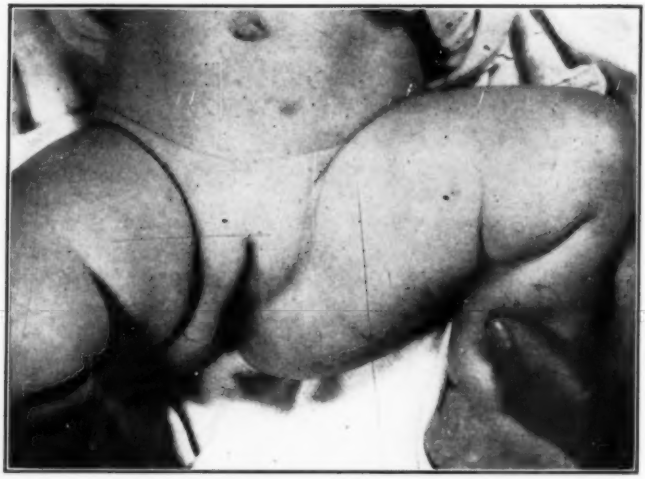

Fig. 2. Note limitation in abduction of the right thigh. On the contracted side the groin crease is deeper.

manifested by pain, fatigue, stiffness and limp in adult life. In the luxated type, the head of the femur is out of the socket. These are the cases, if not corrected before standing, that invariably become dislocated hips after weight bearing begins; and in spite of proper treatment, after the standing stage, result in a low percentage of perfect cures; whereas, if detected and treated pre-standing, correction is obtained in a high percentage.

Etiology. The etiological factors are controversial. There is a concept of a genetic defect whereby there is interruption of normal

intra-uterine growth involving the hip joint. What the factors are or why there is a predilection to involve hips without other joints cannot be stated. There is a small percentage in which there may be some concomitant deformity, such as club feet. At times, one finds repetition of this deformity in some phase in certain families. A mechanistic theory is propounded whereby extrinsic forces may cause undue pressure which results in hip dysplasias. It is interesting to note several factors which may tend to substantiate the

Fig. 3. Note bulge on left that extends from the crest of the ilium to upper thigh. The groin crease is more prominent.

effects of abnormal forces. The incidence of hip dysplasias are more prevalent in breech presentations. Such a presentation may prevent the normal reaming of the globular head towards the medial concave area of the acetabulum. There is a high ratio of dysplasia in female infants. The female pelvis is broader and would tend to add a pressure factor on the lower extremities thereby

forcing the growing cartilagenous head of the femur to the outer part of the acetabulum. A constitutional tendency in a pregnant mother is discussed by some authors. It is contended that nutritional and biochemical changes incidental to pregnancy may be a cause. No known disturbance can be stated.

Diagnosis. Early recognition offers the best solution for restoration of functional and anatomic results. This justifies the presentation of an orthopedic problem in a pediatric journal. The

Fig. 4. The gluteal and popliteal creases are higher on the affected left side. The pelvis is tilted on the same side, resulting in a prominent bulging in this region.

pediatrician or the general practitioner sees an infant in its early stage. If he recognizes a hip disturbance pre-standing, he can render a great service in preventing deformity by having simple methods of therapy instituted. It may be stated here that on several occasions a mother has brought an infant for examination

stating that she had difficulty in spreading the thighs in washing or powdering the groins. Parents who have had hip problems or know of such situations in their family will bring an infant for examination and findings will at times suggest a dysplasia.

There are several diagnostic signs that one should observe in the pre-standing stage: (1) Note the attitude of the lower extremities. An infant with hip dysplasia usually lies (in unilateral cases) in an attitude of moderate thigh and leg adduction and the foot is frequently maintained inverted, simulating a mild clubfoot. In several cases an infant was brought for examination on account of an everted attitude of an extremity. The clinical findings, cor-

Fig. 5. Left acetabular upward inclination; pelvis tilted. Outward position of epiphysis which is underdeveloped. Restriction in abduction of left femur with equal outward force on both knees.

roborated by X-rays, were that the opposite unsuspected hip was affected (Fig. 1). The everted position can be explained by a rotary outward shift due to adduction-inversion pressure from the dysplastic hip. The everted attitude is easily correctible by exercises and at times with a Denis-Browne splint. (2) Attempts at abducting the thigh are usually restricted beyond one-half range as compared to the opposite extremity in unilateral cases (Fig. 2). In

bilateral cases, the restriction is noted on both sides. (3) In unilateral cases, a prominence or a bulge is noted about the area of the greater trochanter (Fig. 3). In bilateral cases, fullness is seen about both trochanters. (4) An elevation of the crease of the gluteal fold is seen in unilateral cases. This elevation is from one-quarter to one-half inch and a corresponding elevation is noted in the popliteal crease (Fig. 4). (5) At times, on manipulation, particularly on pushing up an extremity, a click may be heard or

Fig. 6. Acetabular index: Base line crosses junction of both ilia. Angular line extends across both ends of the acetabulum to the base line. Angle of incidence on the right is 18°; on the left, 33°.

abnormal movement felt in the affected hip. (6) In older prestanding cases shortening of an affected extremity is apparent when both extremities are extended. If the hips are flexed to ninety degrees with both knees extended, the shortening is overcome. When both extremities are completely flexed at the hips and the knees are extended, the affected extremity becomes longer. The explanation is that a normal hip moves concentrically, so that its position within the hip socket causes equal motion in all directions. In a

dysplastic hip the head of the femur moves on a shallow surface outside of the center of the acetabulum; an eccentric motion results so that when the hips and knees are extended, the affected head is above the hip joint—hence, the extremity is shortened. On complete hip flexion, the head moves below the normal acetabular level, which lessens the distance between the hip and the foot—hence, the extremity is lengthened.

X-rays are important as diagnostic procedures. The roentgenologist frequently misguides the attending physician in that he does not see variations in a routine examination. He must be impressed that minor deviations from the normal may, if overlooked, affect the prognosis. He must carefully note the capital epiphysis in that it is frequently under-developed or fragmented in dysplastic states and may at times be absent. The epiphysis is usually displaced to

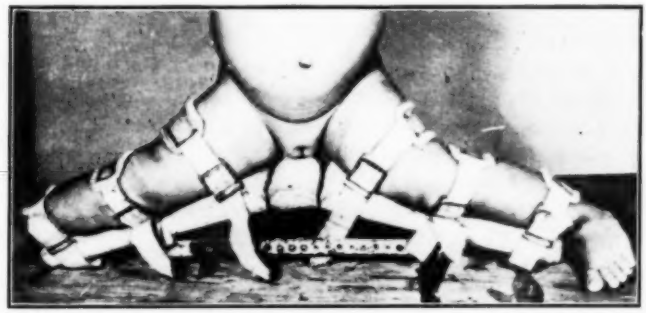

Fig. 7. A modified Putti splint, adjustable to gradually obtain full abduction.

the outer portion of the acetabulum so that part or all of the head may extend beyond the outer margin of the acetabulum. With equal force, on abducting the thighs, an x-ray will show restriction of the outward stance of the femur on the affected side. There is more of a perpendicular incline of the roof of the acetabulum (Fig. 5). It is essential that the roentgenologist note the acetabular index which is an angle formed by its base line crossing both sides of the pelvis and a line connecting both ends of the acetabulum crossing the base line (Fig. 6). Kleinberg and Lieberman[3] have established that an angle up to twenty-seven degrees is considered normal in the pre-walking stage and a measurement of thirty degrees or over is regarded as potential dysplasia.

Treatment. In general, it can be stated that in early postnatal life simple abduction methods will facilitate reposition. In addition to splintage, simple exercises whereby the lower extremities are stretched in abduction are shown the parent. In mild cases a firm pillow is placed between the upper thighs and held in position by a diaper that is pinned to the under shirt. Where the resistance to abduction is moderate and up to about the sixth month, a modified Putti or Ponsetti splint is applied (Fig. 7). If much resistance is encountered, in that adduction and shortening persist, it may be necessary to apply traction to pull down contracted tissues, followed by manipulation and cast application.

Prognosis. Early treatment before standing restores the anatomic alignment of the hip joint so that there is usually no delay in standing and walking at the usual time. Unrecognized dysplasias may lead to arthritic changes in later years or dislocation.

SUMMARY

Hip dysplasia is a congenital anomaly resulting in imperfect articulation between the head of the femur and the acetabulum. Many mild cases are self-limited and self-corrective. Some cases, if not treated, develop late articular changes resulting in osteoarthritis in the adult. A few neglected cases go on to complete dislocation of the hip. The etiology has been considered. Clinical and roentgen diagnostic features are discussed. Early recognition and treatment are stressed to prevent latent deformities.

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CHOLINE IN TOXICOSIS OF INFANTS. (Revista di Clinica Pediatrica, Florence, 46:487, Aug. 1948). Gentili and Tangheroni believe that toxicosis from functional insufficiency of liver is the most important factor in gastroenteritis of infants. They report favorable results from administration of choline hydrochloride in 25 cases. The drug was given twice daily by intramuscular injection. A 2 per cent choline hydrochloride solution was used in fractional doses of 2 cc., up to a daily dose of 4 cc. for four, six or ten consecutive days.—*Journal A.M.A.*

THE USE OF RICE AS A CEREAL FOOD IN INFANTS*

A Clinical Study

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In view of the fact that rice forms the major part of the cereal food of half the population of the world, it is surprising that so little attention has been paid to its value in the feeding of infants and young children. In a previous article,[1] we concluded, after a comparative study of cereals used in infant feeding, that rice provided more available caloric energy than equal amounts of other commonly used cereals.

Slobody[2] et al., in a comprehensive study of rice sensitivity, found an extremely low incidence of any form of allergic reaction to rice preparations used in infant feeding.

Shulman[3] states: "I prefer the introduction of cereals in the form of rice, the least allergenic of all cereals." He also advises the use of a single cereal in preference to combinations, such as those found in many of the prepared cereal foods.

The present paper is a preliminary clinical study of the value of rice as a cereal food in a group of normal children carefully observed on the wards of Metropolitan Hospital. A group of seventy-eight children were studied. Of these, forty-seven, our experimental group, were fed on rice cereals and a control group of thirty-one infants were fed with other standard cereal preparations. The infants ranged in age from nine days to eight months and were observed for a time period ranging from thirteen to one hundred and thirty days, as circumstances would allow in each individual case. The variations in the time of observation and the wide range of ages were necessitated because of our source of material. The cases studied were all well-baby boarders subject to irregular and sudden transfers from our ward.

In our study, particular attention was devoted to the following features: height and weight increments, palatability of the cereal preparation used, presence or absence of any abnormal or un-

* From the Frederick S. Wheeler Foundation for Nutritional Research and Department of Pediatrics, New York Medical College, and Flower and Fifth Avenue Hospitals, New York.

toward reactions due to this cereal diet, e.g., colic, diarrhea, constipation, nausea, vomiting, skin eruptions or changes in the number or consistency of stools. Microscopic examinations of stools prior to and following the addition of rice to the diet were done to determine the presence of an excess of microscopic starch granules in the feces.

In the experimental group of infants, regular dietary regimes standard for the particular age groups were used; the ordinary cereals in use were eliminated, and rice substituted. The only deviations from more or less standard dietary procedures were the addition of rice to the diets of all the infants in our group, regardless of age. Thus, the rice-fed group included thirteen infants one month of age, and twelve in the two-month age group, and five infants between eight weeks and one month of age

The preparation used was Cream of Rice, a finely milled rice flour with added thiamin, niacin, riboflavin and iron. This was prepared by cooking with a small amount of evaporated milk, dilute 1:1 or 1:2 with water, and sweetened with a small amount of table sugar, as trial and error proved this to be most palatable. The amounts accepted by the infants, as would be expected, varied with their ages. Small infants took up to one tablespoonful, and older infants accepted from one to three tablespoonfuls at a feeding, with slight individual variations.

In the experimental group, there were no untoward or allergic reactions which could be attributed to the ingestion of the rice cereal. There were no instances of skin eruptions, colic, diarrhea, constipation, nausea or vomiting. The stools remained grossly unchanged in consistency, color and number, but there was an increase in the amount of microscopic starch granules in twenty-eight cases, or 66 per cent, as compared to the amounts found in their stool specimens before they were started on rice. All these children gained weight, however, and appeared normal, and none gave any clinical evidence of gastro-intestinal or metabolic disorders. In the entire group of forty-seven children, one child displayed poor appetite; in all other cases, appetite ranged from fair to good. The average rate of weight gain for the experimental group, designated in ounces per week, was 4.4 ounces, and the height designated in centimeters per week was .2.

In the control group of thirty-one babies, the weight gain was

4.1 ounces per week. Of the group of thirty-one infants, eight, or 40 per cent, showed small amounts of microscopic starch granules in the stools. These were present in slightly lesser amounts than were found with the rice-fed group. In our series, we have been unable to attach any particular significance to this difference.

Rice as a cereal food appears to be well tolerated by infants, including the very young age groups below three months of age, with no occurrence of allergic or gastro-intestinal disturbances. Its value as a substitute or supplement to other cereal foods deserves attention.

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RESPIRATORY DISTURBANCES IN POLIOMYELITIS. (Deutsche medizinische Wochenschrift, Stuttgart, 73:508, Nov. 5, 1948). Aschenbrenner and Dönhardt report 228 patients with poliomyelitis; of these, 31 with severe respiratory disturbances were admitted to the Altona Hospital during the poliomyelitis epidemic in Hamburg in 1947. Only 6 of the 31 patients were less than 15 years of age, while 25 were between the ages of 16 and 42. The mortality rate of the entire group of 228 patients was 11.8 per cent. Nineteen of the 31 patients died before the initiation of the treatment in the iron lung. All of them presented the spinal type with mechanically conditioned hypoventilation. The remaining 12 patients were placed in the iron lung; 7 of them died during the first week. Treatment in the iron lung came too late for 3 of these patients who had already been moribund, while the other 4 had severe combined bulbospinal respiratory disturbances with pneumonia. Four patients recovered and could be discharged from the hospital with fairly adequate respiration. One of the fatal cases was that of a girl, aged 15; death from acute heart failure occurred suddenly on the sixty-sixth day of the disease after three bouts of pneumonia had been controlled with penicillin. Careful control of the heart and early treatment with strophanthin may be of decisive importance. Temporary, reversible paralysis of respiratory muscles is the chief indication for treatment in the iron lung.—*Journal A.M.A.*

AMIGEN-DEXTRI-MALTOSE FEEDING OF THE NEWBORN*

Preliminary Report

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This is the report of a modified feeding program conducted on 156 newborn infants delivered at the Elizabeth Buxton Hospital, Newport News, Virginia, in an attempt to initiate earlier weight gains. Because of the great demands placed upon this hospital by civilian and military patients, it was necessary to discharge the mothers and infants as soon after delivery as possible; usually the fifth or sixth day postpartum. It was noted that many of our infants were well under birth weight on the sixth day or had only begun to gain following the normal loss that occurs during the first few days of life. Because of this, we attempted to modify the type of feeding during the first four days of life so that a larger percentage of our infants would be closer to birth weight, or, at least, showing substantial weight gains at the time of discharge.

It was not our intention to attempt to prevent entirely the weight loss that occurs during the first few days of life. As pointed out in the literature, usually 7-10 per cent of the body weight is lost and there is no advantage in preventing this unless the loss exceeds 12-15 per cent.[1] It has also been pointed out that 25 per cent of the newborn infants regain the weight lost by the end of the first week and about 50 per cent by the tenth day.[2] It has been suggested in recent literature that a synthetic protein-salt-carbohydrate mixture, in which the protein is not of human origin, may be of value in infant feeding.[3]

In an attempt to initiate an early gain in weight, the following procedure was carried out:

Two groups of infants were studied. The control group (Group I) is represented by data obtained from 156 unselected cases born prior to the introduction of our modified feeding program. All the infants in Group I were breast fed, supplemented with 5 per cent Dextri-Maltose No. 1 for the first four days of life. This

*Materials for this study provided by Mead Johnson & Co., Evansville, Ind.

group is composed of 78 males and 78 females. The experimental group (Group II) is composed of 156 infants, 78 males and 78 females. These infants received 5 per cent Amigen, 5 per cent Dextri-Maltose No. 1 solution every four hours (2 ounces) for the first twenty-four hours, then breast feeding supplemented by the same solution for the next three days. After the fourth day, the supplementary feeding was stopped. The majority of the infants in both groups were discharged on the sixth postpartum day and we arbitrarily chose the first six days of life for the compilation of data.

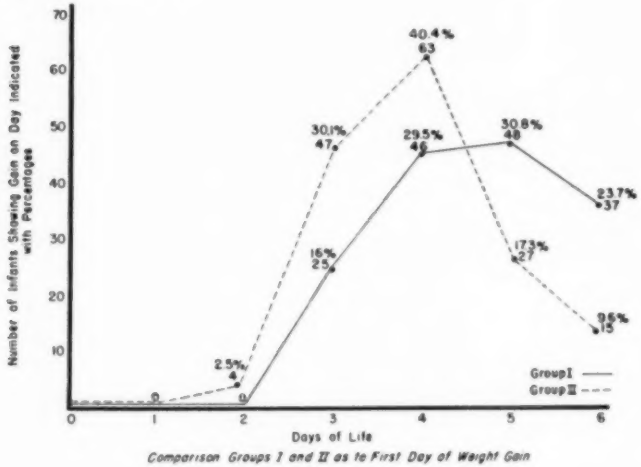
Because of the recent successes with predigested feedings, we selected Amigen as the agent best suited to our needs.[4, 5, 6] One ounce of 5 per cent Amigen solution supplies 5.85 calories together with certain amounts of electrolytes normally present in the blood.[7] The 5 per cent Dextri-Maltose solution furnishes 5.62 calories, so that one ounce of the final solution supplies 11.47 calories. Amino acid mixtures are absorbed easily and promptly from the intestine and in the normal individual 72-98 per cent is absorbed within thirty minutes when placed directly in the intestine.[8] With reference to protein sensitivity, the antigenic qualities of protein are said to be destroyed during the enzymatic digestion which takes place in the production of the amino acids present in Amigen.[9]

DISCUSSION

It is evident from Table I that there is only a slight difference in the weights of Group I and Group II on the sixth day of life. We feel that this is partially explained by the fact that nine of the infants in Group II, showing gains on the third and fourth day, experienced a loss in weight on the fifth and sixth day after the supplementary feeding was stopped on the fourth day. There was no illness in the mother or infant to explain this weight loss.

None of the infants in Group II have shown any evidence of sensitivity to date. It was not necessary at any time during this study to stop the Amigen-Dextri-Maltose feeding because of regurgitation or loose stools. It was noted that this mixture was not palatable and some difficulty was encountered in getting the infants to take the feedings. It was also noted that the infants

who showed gains on the third and fourth day of life, took on the average of four to seven ounces per twenty-four hours for the first four days. Infants taking less than this amount did not show early gains in weight.



Comparison Groups I and II as to First Day of Weight Gain

FIG. I

	Group I	Group II
FEMALES		
Number of Cases	78	78
Average Birth Weight	6 lbs. 15 oz.	7 lbs. 0 oz.
Average Maximum Weight Loss	8.24 oz.	8.33 oz.
Average Weight on 6th Day	6 lbs. 13 oz.	6 lbs. 7 oz.
Number of Cases of Birth Weight 6th Day	4	7
MALES		
Number of Cases	78	78
Average Birth Weight	7 lbs. 12 oz.	7 lbs. 2 oz.
Average Maximum Weight Loss	9.4 oz.	9.3 oz.
Average Weight on 6th Day	6 lbs. 6 oz.	6 lbs. 9 oz.
Number of Cases of Birth Weight 6th Day	2	3
TOTAL		
Number of Cases	156	156
Average Birth Weight	7 lbs. 5 1/2 oz.	7 lbs. 1 oz.
Average Maximum Weight Loss	8.22 oz.	8.8 oz.
Average Weight on 6th Day	6 lbs. 8 oz.	6 lbs. 8 oz.
Number of Cases of Birth Weight 6th Day	6	10

TABLE I

It is felt that Fig. I indicates a definite difference in the two groups, showing that the experimental group (Group II) tended to gain weight sooner than the control group (Group I).

CONCLUSIONS

While the group reported is small, we feel that the marked difference in the two groups, as shown in Fig. I is significant and warrants further investigation.

Although the infants taking the Amigen-Dextri-Maltose solution gained well, there was little difference in the groups at the end of two weeks. It was also evident from observing these infants that they could differentiate the two supplementary feedings used. The majority of infants showed a dislike for the Amigen-Dextri-Maltose mixture, while only a few showed any dislike for the Dextri-Maltose solution without Amigen.

SUMMARY

A solution of 5 per cent Amigen-5 per cent Dextri-Maltose supplying a total of 11.47 calories per ounce was used as a supplementary diet every four hours for the first four days of life in 156 breast fed infants in an attempt to initiate early weight gains prior to discharge from the nursery. Compared with a control group of 156 breast fed infants supplemented with 5 per cent Dextri-Maltose solution every four hours, the experimental group tended to gain weight sooner. However, no difference in weight could be found when comparing these groups at two weeks or at one month of age.

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LOCAL STREPTOMYCIN THERAPY IN TUBERCULOUS PLEURISY. (Rivista di Clinica Pediatrica, Florence, 46:509, Aug. 1948). Nassi reports good results in 24 children with clinical diagnosis of the disease which was confirmed by the Mantoux test, positive cultures and biologic tests of the pleural liquid for tubercle bacilli. The treatment consisted of thoracocentesis and injection of the drug. Thoracocentesis should be liberal and in some cases repeated. The dose of streptomycin injected locally varied between 200 and 300 mg.—*Journal A.M.A.*

CLINICAL REVIEW

In order to encourage the writing of clinical articles by recent graduates or senior medical students, the ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Reuel A. Benson, New York Medical College, New York; Doctor Philip Moen Stimson, Cornell Medical School, New York, and Doctor John A. Toomey, Western Reserve University Medical School, Cleveland. Other interested medical schools are cordially invited to submit student papers for consideration.*

CLUBBING OF THE FINGERS*

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Clubbing of the fingers is a condition which is so commonly met with in all divisions of medicine; a phrase which in many instances is so loosely applied, so multifariously construed and as a clinical sign often so nebulously taught at the bedside, that it might not be remiss to discuss this entity not only from the viewpoint of occurrence, etiology, pathogenesis and their concomitancies but also from the standpoint of the necessity for more standardized diagnostic criteria.

To approach a subject as replete with conflicting reports, experiments and conclusions as is clubbing in particular and its addended manifestations of osteoarthropathy or achropachy in general, it is perhaps best to analyze the entity in a distinctly categorized fashion and thus begin with a brief history of clubbing as it has progressed from its inception with Hippocrates in the Fifth Century B.C.

From the time that Hippocrates described clubbing in what were apparently cases of empyema, there was no systematic tabulation of its occurrence until in 1832 Pigeaux[1] provided a rather detailed description of the syndrome in connection with a number of cases of tuberculosis. Subsequently, isolated and mostly uncorroborated examples of clubbing were reported sporadically, as occurring with a great number of diseases, chiefly centering in the chest, until within the two-year-period of 1889 and 1890 both VonBamberger[1] and Marie[1], working separately, began the modern investigation of the entity which, although having been the repository for an

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endless number of names, still is most well-known as Marie's hypertrophic pulmonary osteoarthropathy. Marie's series of cases, incidentally, was also the beginning of the differentiation of acromegaly from clubbing since it had been hotly contested that one of Marie's better examples of this condition was a prime case of acromegaly; but even as late as 1941 a report by Brugsch[2] of a patient to whose condition he has ascribed the self-devised syndrome of achropachydermia with pachyperiostitis, reveals the difficulty in classifying the atypical cases of both conditions, as well as the confusing element injected by the possibility of an hereditary basis in cases which show no delineable precursory pathology.

Locke[1], in 1915, firmly established osteoarthropathy as an entity and further ramified the existing classifications under which it fell as a secondary disease. From that time forward a great many workers added mightily to the clarification of the syndrome, introducing extensive clinical and experimental data not only in respect to the acquired form but in the hereditary form as well, until, in 1941, Mendlowitz,[1] in a brilliant and detailed analysis of all phases of previous reports and investigations, including his own work in the field, reset the problem on a more succinctly lucid basis, as shall be seen from his classification and experimental studies which are incorporated here.

Hypertrophic pulmonary osteoarthropathy, as defined by Carr[3] in 1924, is a disease of secondary nature occurring in the course of various chronic conditions, characterized clinically by enlargements of extremities with clubbing of fingers and toes, thickening at joints and in the soft parts, especially of the distal phalanges, and proliferative processes of the periosteum, especially at the lower ends of bones. Ryearson and Sacasa[4] add pain and swelling as commonly seen accompaniments whereas Mendlowitz[1] finds these symptoms to be much more infrequent; as Mendlowitz defines it, the osteoarthropathic element of clubbing is merely an extension of the pathological process to more proximal parts of the extremities, thus predicating the point of view that the fingers are the areas of primary involvement, an hypothesis which many previous authors have found controversial.

Before describing the conditions which give rise to clubbing, differentiation must be made between the several varieties which have been reported down through the years and are now conceded

to be distinct and separate, not alone in occurrence, but as to mechanism of production as well. To completely classify clubbing —which being synonymous with pulmonary osteoarthropathy, even though the use of the word pulmonary in conditions etiologic which have no relation to lung pathology is paradoxical—one must first promulgate the anatomical variancies as separate headings, and thus there is the symmetrical, the unilateral and the unidigital type of clubbing. Further, the symmetrical may be subdivided into hereditary and acquired, and, finally, clubbing must be classified as to its relation with whatever underlying disease is present. Specifically speaking, the acquired symmetrical type is usually what is meant when the term clubbing is used and is the prototype included by Marie in his designation of "L'osteoarthropathic hypertrophiante pneumique." It is the most common form of digital enlargement, the unilateral following it in frequency, with the unidigital being the rarest.

The unidigital type of clubbing may be disposed of by saying that in most reported cases, of which there have been very few, the clubbing has succeeded an injury of some sort or another, to the arm; the classical example being damage to the median nerve from a crushing injury, with subsequent development of unidigital clubbing accompanied by trophic changes[1].

The symmetrical acquired form has been well known to medicine throughout the ages but as West[5] has said: "We know clubbing so well that we are inclined to be persuaded that we know more about it than we really do." Thus the theories of etiology have been as numerous as the reported conditions to which clubbing has been proscribed secondary.

It is well-known that many pulmonary conditions give rise to clubbing in addition to the classical empyema, although this is one of the commonest precursors. Locke,[6] in 1915, discussed the lung conditions which from his survey of the literature and his own cases most frequently gave rise to clubbing and found that the commonest conditions were, in order of frequency: Bronchiectasis, tuberculosis, empyema, lung abscess and malignancy of the lungs and mediastinum. In 1920, Bryan[7] reported one of the first cases of sarcomatous metastates to the lung accompanied by clubbing. Compere, Adams and Compere[8], who have done so much work in the field of osteoarthropathy, reported in 1935 a

case of blastomycosis of the lung which showed pronounced clubbing and other osteoarthropathic changes. Mendlowitz,[1] in summing up the role of the lung as a primary fertility for the creation of secondary clubbing, opined that any condition which gives rise to a chronic pneumonitis, such as the pneumoconioses, atalectasis, via intrabronchial obstruction or external compression of the lung by many things as well as chest deformity, can instigate the occurrence of clubbing; he also gives as further example the variation in frequency of this entity in Ayerza's syndrome, it being common in the chronic pneumonitic type and exceedingly rare in the endarteritic type.

Further conditions of the lung which may give rise to clubbing are congenital lung cysts; Montuschi,[9] in 1938, reported such instances and also remarks that perhaps many idiopathic cases of clubbing might not be considered so if the lungs were investigated more fully in every osteoarthropathic case. Emphysema,[1] a diffuse condition of the lungs, is, surprisingly, not commonly associated with clubbing unless there is attendant bronchiectasis and this further focuses a strong suspicion as to the possible role infection may play in the production of clubbing; for in a scanning of the pulmonary causes of osteoarthropathy one of the most noteworthy things which almost all the conditions share in common is a toxic focus of chronic inflammation in the lung. There is of course the possibly concomitant factor of circulatory discrepancies in evidence in the pulmonary bed as well. Clubbing is very rare in the acute conditions of the lung,[1] being almost negligible in the pneumonias and bronchitides; however, when one includes the thoracic cage as domain for pathology the number of conditions which may give rise to clubbing is extended greatly. Expanding aneurisms of the aorta and its main tributaries as mentioned by Rodgers[10] may produce symmetrical clubbing although it is unilateral in the greater percentage of cases. The numerous mediastinal neoplasms, lymphoblastomata, dermoids and neuroblastomata have been recorded as producing clubbing and of course in cyanotic congenital hearts, subacute bacterial endocarditis and in other architecturally deranged hearts, clubbing is infamously evident. Miller,[11] in 1939, reported a case of clubbing with some generalized osteoarthropathic manifestations in an instance of carcinoma of the thymus.

It is interesting to note that while in a great many quarters it is taught that tuberculosis is a rare cause of clubbing the literature does not bear out this somewhat popular fallacy. Gilmore and Black,[12] in an exhaustive survey of the clinical material in a large tuberculosis center, have found early clubbing in 75 to 95 per cent of their cases, and pronounced soft tissue hypertrophy, not exclusively confined to the fingers and toes, but in many other regions as well, in 65 to 80 per cent of cases. They do however concede that bony changes or more specifically the generalized osteoarthropathic changes are more often seen in the more violent cases of the disease. They also conclude that there is no difference in the osteoarthropathic manifestations dependent upon whether the patient has had tuberculosis for a long or short time and Mendlowitz[1] bears this point out in his statement that he has seen clubbing develop within three to six months of the onset of tuberculosis.

In heart disease, clubbing has been a conspicuous and diagnostically important element for over thirty years. One of the early major investigations in this phase of cardiac pathology was initiated by Cotton,[13] who, in 1922, in a series of 798 cases of organic heart disease, assembled 63 cases of clubbing and further reported that of these, 44 were definitely proven instances of subacute bacterial endocarditis. Of the other 19 cases, four were distinctly probable endocarditis and in the other 15 no signs of endocarditic involvement could be elicited. In connection with the 15 cases which manifested no endocarditic signs, the most frequent architectural disorder was a mitral stenotic lesion and most of these patients were poorly controlled cases of chronic congestive failure. Mendlowitz[1] mentions an instance of clubbing in a case of congestive failure due to Grave's disease; thus as an occasional cause of clubbing can be included congestive heart failure. Cotton [13] concludes from his study of clubbing in cardiac diseases that this digital manifestation is one of the most valued of signs in subacute bacterial endocarditis, far surpassing many of the more prominently advertised signs of the disease in frequency of occurrence and from later clinical studies his fervor in this respect has been borne out.

In 1927, Sprague and White,[14] writing on congenital heart disease, discussed the types of structural anomalies with which

clubbing is commonly associated and concluded that the tetralogy of Fallott, Eisenmenger's syndrome and the coupling of pulmonary stenosis and an interventricular septal defect are the prime congenital conditions associated with osteoarthropathy with the exception of developmental defects which, in terminal stages of failure, allow for reversal of arteriovenous flow in the heart, and also the superimposition of subacute bacterial endocarditis upon a congenital anomaly. They also propose that clubbing is of most suspicious diagnostic implication in cardiac cases and frequently will point to anomalies of architecture.

It is upon leaving the confines of the chest that widespread and highly divergent conditions have been implicated as causative or primary in the development of osteoarthropathy; certain of these conditions being definitely and frequently associated, others reported sporadically and perhaps unreliably due to confusion in criteria for diagnosis as well as incomplete investigation of anatomical areas more prone to enshrine the etiologic pathology.

One of the most common extrathoracic diseases which stands precursory to clubbing is ulcerative colitis, and Schlicke and Bargen,[15] in a review of intestinal causes of osteoarthropathy, report that Teleky's case associated with dysentery was the first instance of such reports. Bensaude and Hillemand and Augier[15] subsequently added three cases in connection with polyposis of the colon. In 1932, Lemerre and Levesque[15] reported a case following amebic dysentery, two more reports appearing in 1937. Schlicke and Bargen remark, however, that clubbing is so frequently seen with ulcerative colitis that it no longer causes any surprise. In their series over a period of two years seven patients with ulcerative colitis evinced clubbed fingers, with only one patient having osteoarthropathy to such an extent that skeletal changes other than digital were demonstrable. The duration of the bowel complaints was nine months to ten years with a two to four year average. The authors note that all cases were poorly nourished and anemic and suggest the sole factors, possibly etiologic, were debility and absorption of toxins.

Mendlowitz,[1] in addition to these intestinal conditions, adds cases of regional enteritis, intestinal tuberculosis, intestinal Hodgkin's, carcinoma of the colon, pyloric obstruction, clubbing subsequent to ascariasis (with subsidence of clubbing after elimination of the worms).

Mention of intestinal conditions must include the celiac syndrome in which clubbing is quite common.

Perhaps the second most common extrathoracic cause of clubbing is disease of the liver—most frequent in Hanot's cirrhosis and rarest in Laennec's but present in a great variety of hepatic afflictions.

Clubbing has been reported secondary to chronic cystopyelitis[1]; subsequent to myxedema following thyroidectomy in Thomas's case,[16] who remarks on the somewhat similar report by Schimer in 1923; and while clubbing is surprisingly seen to be rare in polycythemia vera it is quite frequently noticed in the secondary variety.

In the past a great many other conditions have been named as responsible for clubbing, including syphilis, rickets and syringomyelia; but, with more expert appraisal of cases, a differentiation of these conditions has been made and no longer is "la main succulente" indicative of the trophic changes of syringomyelia, regarded as a feature of osteoarthropathy. Similarly, neither are the clinical or X-ray changes of lues and rickets any longer deemed part of the syndrome.

Isolated cases, such as the one reported in which leprosy[1] was the only delineable concomitant disease entity, are confusing from the point of view of investigations and analyses directed at the unearthment of a common etiologic basis for osteoarthropathic changes and as has been predicated by various workers, in such cases it is frequently difficult to exclude chest pathology.

Throughout the literature the case reports of familial ideopathic clubbing and congenital ideopathic clubbing are fairly frequent with but one notable instance of any mention of an hereditary basis (Seaton[17] in 1938) who paralogistic to the title of his article ("Familial Clubbing") points out that the anomaly was present in three successive generations of one family. Seaton describes his report as the second instance of such hereditary digital changes progressive through three generations but states that six other cases are recorded in the literature where two successive generations were afflicted. Therefore, as Mendlowitz[1] has suggested, this type of clubbing should be simply spoken of as hereditary and most of the cases where the deformity has been present since birth and signs of precursory or accompanying disease are absent should

be similarly titled, for, as Neurath[1] and Bryan[1] and later Mendlowitz[1] have asserted, this digital characteristic is in these cases inherited as Mendelian dominant. Witherspoon,[18] in his report of the first negro child with hereditary clubbing, corroborates this viewpoint.

In respect to hereditary osteoarthropathy, Brugsch's[2] case of achropachydermia with pachyperiostitis which evinced leprous furrowing of the face suggestive of some of the facial changes seen in the osteoarthropathies of tuberculosis from Gilmore's and Black's[12] series, if assumed to be, as Brugsch himself finally conceded, an hereditary form of osteoarthropathy (actually he was more in favor of the other reported cases of hereditary clubbing being incorporated under the banner of his own syndrome) then it would suggest that hereditary forms may not be exclusively confined to the digital areas in manifestation of osteoarthropathic changes, even though Ryearson and Sacasa[4] state rather emphatically that hereditary forms progressive from clubbing alone to hypertrophic osteoarthropathy in general are exceedingly rare. Until now it has been believed that only the fingers and toes could be involved in these cases.

Unilateral clubbing was reviewed in 1941 by Rodgers[10] and of 29 cases in the literature 24 of these were due either to aneurisms of the subclavian, the innominate or the aorta. Of the other five, all had complicating pressure mechanisms to account for the clubbing, such as chronic dislocation of the shoulder and carcinoma of an upper lobe bronchus; in addition Mendlowitz[1] mentions one case of brachial arteriovenous aneurism and one case of phlebectasia as causative of unilateral clubbing. With all these cases Rodgers placed great emphasis on the circulatory changes in the affected extremity, the symptoms of venous dilation and congestion bespeaking his attention entirely; Mendlowitz, however, found no changes in blood flow with his cases. Whatever the etiologic mechanism, suffice it to say that aneurism as a cause was clearly demonstrable in that ligation caused complete retrogression of the clubbing.

At this point it may be of value to mention that at the present time there is complete unanimity of opinion in regard to the incorporation of simple clubbing of the fingers with generalized osteoarthropathy, concomitant joint, soft tissue and periosteal changes,

as one disease entity. In the past it had been variously believed that the generalized skeletal and digital changes were separate and apart, but since Rypins[19, 35] instituted the conception that clubbing was in most cases the primary stage of the disease with simple soft tissue changes found at the onset, followed by digital bony changes and subsequently by generalized skeletal osteoarthropathy and widespread soft tissue perversion, the disease has lately been approached along these lines. The confusing element all along has of course been the comparative rarity of generalized osteoarthropathy and the relatively common occurrence of clubbing.

In respect to simple clubbing without bone changes, and in absence of a recognizable cause, a division must be made between the unsuspected heriditary cases, those with silent lung lesions and actual idiopathic cases. With the infrequent occurrence of such supposedly idiopathic cases reliance must for the time being, as Mendlowitz has conjectured, be placed on the complete lack of autopsy records in these so-called idiopathic cases[1] and thus perhaps tacitly include such cases with either of the other two divisions.

Osteoarthropathy may occur at any age, and, although the number of cases reported of pediatric status is rather limited, the reason for this is obvious in that it is the chronic type of primary disease which is antecedent to osteoarthropathy and it is naturally in the older age groups that the great majority of such diseases are more prevalent.

In addition, Kennedy[20] states that in infants and children, although clubbing is frequent, associated skeletal changes are rare and as explanation for this he offers the theory promulgated by Locke[1] that osteoarthropathy usually develops three to four years after the appearance of the primary disease while simple clubbing occurs much earlier. Whatever the reason, the literature on osteoarthropathy in children is scant, perhaps due to the fact that simple clubbing, so frequently encountered, is dismissed without benefit of skeletal x-ray studies; thus since Von Bamberger's[29] seven-year-old patient with congenital heart disease and clubbing, research reveals but 14 cases of non-hereditary generalized osteoarthropathy. The youngest patient was the 28-month-old case of Hyman's and Herrick's[21]. The primary diseases involved were

congenital heart anomalies, tuberculosis with subsequent pertussis and bronchiectasis, five cases of cirrhosis of the liver, chronic bronchitis, empyema, and in 1927 Marcus'[6] case with what appears from the description to be a possible cystic fibrosis of the pancreas, with subsequent bronchiectasis.

Rypins, in 1935, appraised many of the frequently seen cases of idiopathic clubbing[19] as being due merely to the easily provoked hyperplastic tendencies of mesodermal tissues in the young, but Kennedy[22] and others comment that not only should the skeleton be x-rayed for evidences of osteoarthropathy but intensive investigation of lungs, mediastinum, heart, liver and intestinal tract should be instituted until the case may be either consigned to the hereditary group or to the rapidly diminishing idiopathic group.

Sex, climate, racial and other distributions are apparently not contingent upon the osteoarthropathy but upon the primary disease to which clubbing is sequela.[1]

Anatomically and pathologically there have been many disputations both as to gross and microscopic findings in the involved areas, but this is perhaps primarily due to the paucity of autopsy material. There is general agreement that the essential changes consist of subperiosteal new bone formation in almost any bone but usually in the lower ends of the radius, ulna, tibia and fibula; any bone may be and has been reported to have been involved. Rypins[19] describes it further as a rarefying osteitis with fatty changes in the marrow as well. Villous arthritides with sterile effusions have been reported and while bony changes in the terminal phalanges have been described for decades as being a burring or osteophytic involvement of the tips of these phalanges—in other words a reaction similar to the skeletal changes elsewhere, Compere, Adams and Compere[8] deny this possibility, predicating their contention upon their statement that the terminal phalanges have no periosteum and therefore cannot be said to take part in such a reaction.

The soft tissue perversions in osteoarthropathy are most apparent in the elastic tissues of the involved site but in the fingers all tissues share in the proliferative debauch. The tissues most frequently involved are fingers, toes, nose, ears, malar processes and the soft parts over tibia and fibula.[12]

Clinically, the development of osteoarthropathy is usually in-

sidious with at first only soft tissue changes, confined to the fingers and toes and then typically, osteal procedence to the lower ends of the long bones of the extremities. There are several types of involvement described: With soft tissue clubbing of phalanges alone; with skeletal changes and no clubbing (rare); with soft tissue clubbing and phalangeal bony changes; with soft tissue clubbing, phalangeal and other bony manifestations. Associated changes, as have been mentioned, may occasionally occur in the joints when the accompanying osteitis reaches the end of the bone. Edema of the legs is a fairly frequent finding in osteoarthropathy and gives suspect to underlying bony patholgy. There is occasionally pain over the site of the involement when the osteoarthropathy develops in a rapid manner and rarely there is a feeling of warmth in the fingers. Clubbing as described by Lovibund[5] can occur as early as 10 days in cases of lung abscess, but usually takes weeks or months and thus the characteristic digital changes occur slowly, so that frequently in early cases the diagnosis is missed and it is not until the classical drumstick fingers are present that the diagnosis is pounced upon. Therefore, in respect to the fingers and toes a more detailed developmental description may be in order. Clubbing is usually first seen in the thumb and index finger and subsequently spreads to involve all phalanges. The pathological process begins at the nail root, just beyond the interphalangeal joint, as a hard transverse ridge on the dorsal aspect of the digit, and the overlying skin is very smooth and shiny. The longitudinal ridging of the nail often tends to be prominent and the nail may be quite brittle, in fact, there is one reported case of complete nail necrosis.[1] There is an increased rate of nail and cuticle growth and hangnails and paronychia are commonly observed. Early there is a vascular turgescence of the nail bed with first a hyperpink tint to the nail bed and subsequently a lilac to cyanotic shading as the clubbing progresses; the cyanosis appears more markedly when the fingers are cooled.[18] Subsequently, the base of the nail becomes elevated so that its outline may be seen beneath the skin and, in far advanced clubbing, the nail floats and can be rocked back and forth in its bed. In cases of long standing the fingers may show a hyperextensibility of the terminal phalanx.[5] It must be remembered that muscular wasting frequently accentuates the clubbing. None of the above manifesta-

tions must be omitted in a diagnostic search for early clubbing but the definitive diagnosis rests upon one salient feature so aptly emphasized by Lovibund.[5] It is the "profile" of the nail which is so important, and the angle of that profile is the basic element in correct diagnosis. Normally the angle of the nail with the finger is 160 degrees and regardless of deformities of the nail itself, curving, spatulation etc., it is solely a disturbance of this angle on which the diagnosis of clubbing—early or late—rests; so that in any attempt to diagnose early clubbing this angle must be distorted to more than 160 degrees to provide proof positive of osteoarthropathic changes. Therefore, many of the descriptions of parrot nails or beaking or curving or drumstick deformities which have been loosely applied as diagnostic of clubbing were only concomitant and not necessarily constant features of the disease—for nail deformity does not of itself bespeak clubbing. In a differential diagnosis of clubbing, normal anatomical variations must be taken into consideration first and subsequently chronic paronychia, which exhibits chronically swollen soft tissues at the base of the nail, not in the nail bed; usually non-symmetrical as well and the nail angle is undisturbed. Haberdeen's nodes are bony swellings distal to the interphalangeal joint which excludes them from possibility. Subungual whitlow will resemble clubbing but is confined to one finger. Under the X-ray, the earliest phalangeal changes are increased flaring of the ungual processes of the terminal phalanges, going on to burring, and occasionally to progressive osteoporosis with complete resorption, and these manifestations may occur in any other bone.

Other systemic changes mentioned from time to time as accompanying clubbing, such as increased sweating, muscle weakness and osteoporosis to the point of pathological fracture[1] are probably as much allied with the primary disease entity as they are with osteoarthropathy alone, and delineation of exact allegiance is difficult.

It is probable that prolonged clubbing never disappears but the numerous reports of subsidence of the phenomenon in exceedingly short intervals of time with cure or circumvention of the primary pathology gives credence to the etiologic bearing such pathology has in the production of the clubbing. In many cases the clubbing exacerbates and remits as the course of the primary disease

waxes and wanes[23]. Complete disappearance is never of course seen in the hereditary form.

Ryearson and Sacasa[24] postulate the possibility of certain of the reported idiopathic cases being merely osteoarthropathic residua of a disease which has been recovered from, and although this has not been verified it seems to be a rather logical deduction and may further reduce the number of cases relegated to the idiopathic category.

When one reaches etiology and cause of osteoarthropathy one releases a boiling torrent of verbiage—signifying for the most part very little. Mendlowitz[1] and West,[1] approximately two decades apart, came to the conclusion that in respect to mechanism of production the sum total of what was known was nothing. Beginning with Marie and Von Bamberger and extending to the present day there are the adherents to the circulating toxin theory and Von Bamberger unsuccessfully injected sputum from clubbing sufferers into animals to attempt recreation of bony changes.[25] Thayer[8] believed clubbing to be part of amyloidosis and was supported in his contention by one case of hepatic amyloidosis with clubbing. Massalongo[25] thought it occurred only in the cases of arthritic diathesis, while Thorburn[8] believed the appearance resembled new bone formed around bones adjacent to a tuberculous joint. Berent[8] clung to his nerve disease theory as long as syringomyelia was an acceptable cause of clubbing. A multitude of workers, including Hyman, Herrick and Bryan,[21, 7] believed in the mechanical factor of blood stasis. Marcus[6] and Phemister[25] combined chronic toxemia with circulatory disturbances from either cardiac or lung involvement and Phemister[8] also experimentally worked on streptococcus injections, but failed to produce any results. Compere, Adams and Compere[25] made the most intensive attack on the subject when they attempted to support their theories of pulmonary and peripheral vascular discrepancies by producing intrathoracic complications in dogs. They produced pleural effusion, atalectasis, lung abcesses, bronchial stenosis, and foreign body irritations but achieved no clinical, nor x-ray, nor laboratory results—there being no change in H ion, calcium phosphorus or carbon dioxide content of the blood.

That it is possible for such animals to develop osteoarthropathy is well demonstrated by several reports of clubbing changes with

autopsy findings in dogs, cats and even a lioness[26] where tuberculosis was the usual precursory pathology.

It was not until Mendlowitz[1] effected anastomoses between a left and adjacent main pulmonary artery to a left auricle in dogs, that experimental clubbing was produced and yet although this duplicates a shunt similar to one seen in congenital heart disease it does not explain the reason for the occurence of clubbing. It would be easy to say that anoxia is the cause and let it go at that but how explain the lack of clubbing in severe anemias or in the anoxic conditions of the extremities in phlebitic and arteriosclerotic states.

In subacute bacterial endocarditis Stewart,[27] referring to Cotton's investigations,[13] throws light on etiologic factors at work in this particular instance alone. He refers to the cause of the clubbing as a purely embolic phenomenon in terminal capillary loops but as to substantiation of this there is a great dearth of corroborative evidence. Then there is the necessity for explaining clubbing in conditions which are not so intimately connected with the vascular supply to the extremities, such as in liver and intestinal conditions. In the latter the circulating toxin theory might be applicable but then why do not all cases of ulcerative colitis produce the syndrome and this question can apply unfortunately to almost any of the diseases which at times give rise to clubbing; why do not all instances of these diseases cause clubbing and why do some show simple soft tissue changes with severe cases of concomitant disease while others will show generalized osteoarthropathy with milder attendant pathological states.

For the final common denominator investigators attacked the site of pathology itself and began studies of the fingers and arms. Roncato's[1] results of high venous and low arterial pressure in the fingers eventually were found to be erroneous for it is now known that the venous pressure in clubbed fingers is normal. Capillaroscopy, a recent innovation, has given conflicting results due primarily to unstandardized conditions, it being well known that many things in addition to temperature affect the capillary beds, i.e., emotions, pain etc. The blood flow experiments have similar disadvantages and many workers have never been able to support De Haas'[1] contention as to decreased blood flow in the fingers in clubbing. In recent experiments using Stewart's[27] formula and

a finger tip calorimeter it was found that the blood flow per square centimeter was high in clubbing and receded upon subsidence of the etiologic pathology even before a receding of osteoarthropathic changes could be ascertained. This has led numerous authorities to consider that over nutrition of the affected tissues is the one factor demonstrable in all cases of clubbing; and postulating this as the cause of the hypertrophy and hyperplasia, with support from recent evidence of increased peripheral blood flow, investigations may perhaps be able to proceed from this one basic point. It is of course at present difficult even to admit this as basic in all cases of clubbing for how could it explain the cases of clubbing in myxedema subsequent to thyroidectomy; here blood flow should be reduced rather than increased.

In the end it is still difficult to avoid bringing in chronic toxemia as a possible factor when in so many of the widely distributed cases of osteoarthropathy this feature appears as the sole communication between entities as widely divergent as subacute bacterial endocarditis and ulcerative colitis, but then again why should a toxin specifically select only certain areas as a site of predilection.[16]

The answer to these and many other questions remains buried in the research of the future but even if clubbing should remain the enigma etiologically that it is today its importance should be better understood and its diagnosis more logically and confidently made for in any of the disease entities previously mentioned it may be one of the earliest signs and therefore a valuable adjunct to the clinician who in many cases is successful in his therapy only when and to the extent that a diagnosis can be made early and in the incipience of a condition, which if allowed to proceed further, would perhaps reach a stage of either inoperability or firm resistance to whatever therapies are available. Therefore, in conclusion, not only should the syndrome of osteoarthopathy be more scrupulously taught and discussed but clubbed fingers as a definite sign of certain diseases as well as an implication of the possible existence of the more serious later stages of generalized bony involvement, should routinely be investigated more thoroughly both as to the existence of a generalized form of the syndrome and as an indication that disease of some sort lurks in the customary sites of pathological predilection in the body. If such investigations were

to be made a wealth of information would undoubtedly be made available and thus probably aid greatly in the delineation of the true physiologic or physiopathologic mechanism involved as etiologic in this condition.

SUMMARY

1. A brief history of the status of clubbing of the fingers is presented.

2. Clubbing of the fingers and hypertrophic pulmonary osteoarthropathy are synonymous and merely different stages of one entity.

3. With the exception of the hereditary type, pulmonary osteoarthropathy is a disease of secondary nature—the primary pathology usually centering in the lung.

4. Clubbing is classified and the various conditions which give rise to the syndrome are discussed.

5. Clubbing, contrary to popular belief, is common in all types of tuberculosis—early and late— and duration of the disease often has no bearing on its development.

6. Clubbing of the fingers is one of the most valuable signs in the diagnosis of subacute bacterial endocarditis.

7. Diseases, such as rickets, syphilis and syringomyelia, are no longer considered part of the clubbing syndrome.

8. Idiopathic clubbing is now looked upon as either hereditary in etiology or due to undiscovered or healed pathology. The term congenital and familial clubbing should be replaced by the more exact hereditary title.

9. The literature of osteoarthropathy in children is reviewed and variation of the findings in adults and children discussed.

10. The symptoms, signs and diagnostic criteria of pulmonary osteoarthropathy are tabulated and the necessity for basing the diagnosis of the condition upon the angle of the nail with the root exemplified.

11. Theoretical concepts as to etiology and an analysis of the experimental work accomplished preface the one conclusive common denominator accepted in all cases of clubbing today: A hypernutrition of the phalangeal tissues.

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